

Claim objections:

Applicants are also grateful to the Examiner for bringing our attention to clerical errors in the claims. The errors have been corrected as suggested.

All the amendments made to the claims (except for changes in claim dependency) do not alter the scope of what is claimed. Accordingly, coverage is retained for all equivalents for which applicants were previously entitled.

Rejections under 35 USC § 112 ¶ 2:

Claim 41 stands rejected as being indefinite for the manner in which the hybridizing DNA is referred to.

The claim has now been amended in line with the Examiner's suggestion, and tracks the hybridization language in related U.S. Patent 6,475,789. The skilled reader will know when to make appropriate adjustments to obtain stringent hybridization conditions for polynucleotides different from DNA. Withdrawal of this rejection is respectfully requested.

Claims 43, 47, 50, and 66 stand rejected as being indefinite for the manner in which the cell selection step is referred to.

Base claim 41 is a method for increasing proliferative capacity of a single cell. Hence, the selection step should also cause the selection of a single cell. The claim wording offered in this amendment is believed to meet the Examiner's concern, while maintaining proper antecedent basis from claim 41. Withdrawal of these rejections is respectfully requested.

Rejections under 35 USC § 112 ¶ 1:

Claims 41-57 stand rejected as being enabled by the specification for increasing proliferative capacity of a cell *in vivo*. The Office Action asserts that neither the specification nor the state of the art at the time the invention was made teach or suggest how to practice the claimed invention *in vivo*.

U.S. patent application 10/143,536 has been considered by the Examiner, but is not believed to support applicants' submission that the specification is enabling, because it bears a date subsequent to that of the present disclosure.

Applicants are grateful that the Office Action acknowledges that the specification is enabling for increasing proliferative capacity *in vitro*.

However, the Office Action provides no basis for asserting that the claimed invention would not work *in vivo*. The response to the previous Office Action reviewed case law that indicates working examples written into the disclosure are not necessary for a specification to be enabling for the claimed invention<sup>1</sup>. Thus, the specification is enabling for the claimed invention. A further explanation follows.

Analysis of whether the specification is enabling for the claimed invention involves two questions:

1. What does the specification enable?
2. Do the embodiments that are enabled by the specification meet the limitations of what is claimed?

The hTERT vectors described in the specification have been proved to increase proliferative capacity in cultured cells. Since many of these vectors systems have been proven to cause expression of other genes *in vivo*<sup>2</sup>, there is *a priori* evidence that the vectors that cause hTERT expression *in vitro* will also cause hTERT expression in cells *in vivo* — and as a consequence, increase proliferative capacity of cells *in vivo*.

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<sup>1</sup> A specification can adequately describe the manner and process of making an embodiment of an invention, whether or not it has actually been conducted. Use of prophetic examples does not make a patent non-enabling. The burden is on the person challenging the patent to show that the prophetic examples together with other parts of the specification are not enabling. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984).

<sup>2</sup> See, for example, the following articles: The use of adenoviral vectors for gene therapy and gene transfer in vivo. Bramson, Graham & Gauldie, Curr. Opin. Biotechnol. 6(5):590-5, 1995. An in vivo gene therapy approach for experimental proliferative vitreoretinopathy using the truncated platelet-derived growth factor alpha receptor. Ikuno et al., Invest Ophthalmol Vis Sci 2002, 43(7):2406-11. Adenovirus-mediated expression of a truncated PDGFBeta receptor inhibits thrombosis and neointima formation in an avian arterial injury model. Ding et al., Gene Ther 2000, 7(19):1640-7. Targeting endogenous platelet-derived growth factor B-chain by adenovirus-mediated gene transfer potentially inhibits in vivo smooth muscle proliferation after arterial injury. Deguchi et al., Gene Ther 1999 Jun;6(6):956-65. Cochlear function and transgene expression in the guinea pig cochlea, using adenovirus- and adeno-associated virus-directed gene transfer. Luebke et al., Hum Gene Ther 2001, 12(7):773-81. Gene therapy for cystic fibrosis by means of aerosol: Rochat et al., Aerosol-Med 2002,15(2):229-35. Adenoviral gene transfer of aspartoacylase into the tremor rat, a genetic model of epilepsy, as a trial of gene therapy for inherited epileptic disorder. Seki et al., Neurosci Lett. 2002;328(3):249-52. Phase I study of chemokine and cytokine gene-modified autologous neuroblastoma cells for treatment of relapsed/refractory neuroblastoma using an adenoviral vector. Brenner et al., Hum Gene Ther. 2000;11(10):1477-88. A phase I study of adenovirus-mediated transfer of the human cystic fibrosis transmembrane conductance regulator gene to a lung segment of individuals with cystic fibrosis. Zuckerman et al., Hum Gene Ther. 1999;10(18):2973-85. Six-month assessment of a phase I trial of angiogenic gene therapy for the treatment of coronary artery disease using direct intramyocardial administration of an adenovirus vector expressing the VEGF121 cDNA. Rosengart et al., Ann Surg. 1999;230(4):466-70.

Accompanying this Amendment is a Declaration under 37 CFR § 1.132 by Dr. Calvin Harley, Chief Scientific Officer of Geron Corporation. Dr. Harley provides affirmative evidence that hTERT expression can be used *in vivo* with important therapeutic benefit:

- The disclosure as filed describe reagents and methods for expressing hTERT, and the use of hTERT expression to increase proliferative capacity *in vivo*.
- Increasing hTERT expression using standard expression vectors has been shown to cause increased proliferative capacity in a wide variety of cell types *in vitro*.
- Increasing hTERT expression in cytotoxic T lymphocytes improves their cytolytic and antiviral capabilities. Administration of the vector i.v. should transduce CTLs in the same manner it transduces them in culture.
- Experiments done *in vivo* using genetically altered mice lacking telomerase function shows that supplying the missing gene *in vivo* protects them against experimentally induced liver cirrhosis, which is attributable to restoring proliferative capacity of the liver cells.
- Experiments done *in vivo* in an ischemic wound model shows that treatment with a vector to cause hTERT expression increases the formation of granulation tissue at the wound site.
- Experiments done with endothelial progenitor cells shows that hTERT expression causes enhanced telomerase activity, cell migration, and caused increased proliferation by protecting them from apoptosis. *In vivo*, the endothelial progenitor cells enhanced perfusion in ischemic tissue, causing an increase in capillary density.

The results discussed in Dr. Harley's Declaration confirm that hTERT expression in cells causes increased proliferative capacity. hTERT expression *in vivo* in turn causes enhanced tissue repair and other beneficial effects.

Also accompanying this Amendment is a Declaration under 37 CFR § 1.132 by Dr. John Irving, Director of Vector Biology at Geron Corporation. As an expert practicing in the field of vector biology at the time this disclosure was first filed, Dr. Irving indicates that someone of ordinary skill in the art, reading the disclosure of this application, would have the ability to make telomerase vectors capable of increasing proliferative capacity of cells *in vivo*. In particular, he indicates that skilled reader would be able to make an adenovirus vector substantially the same as the vector used in the ischemic ear wound model experiments referred to in Dr. Harley's Declaration.

Thus, the answers to the questions posed earlier are as follows:

1. The specification provides the hTERT sequence, effective combinations of genetic elements. In combination with common practice in the relevant art at the time of filing, this enables the skilled reader to make effective vectors for causing expression hTERT in cells, without undue experimentation.
2. A number of clinical trials have shown promising results for expressing other genes using vectors constructed from adenovirus, retrovirus, and AAV, validating the use of vectors such as those exemplified in the specification for causing gene expression *in vivo*. Vectors for expressing hTERT taught in the specification cause increased telomerase function in transfected cells — thereby increasing proliferation capacity, which is the functional requirement required by the claims. The use of these vectors is appropriate for any application in which increased proliferative capacity is a desirable outcome.

Accordingly, the specification enables the skilled reader to practice the invention as presently claimed. This meets the enablement requirement of 35 USC § 112 ¶ 1. Withdrawal of this rejection is respectfully requested.

#### Double patenting

Claims 41-47 stand rejected under the judicially created doctrine of obviousness-type patenting with respect to claims 7-8 of U.S. Patent 6,337,200. The Office Action asserts that claims 41-47 of the present application are generic to what is cited in claims 7-8 of the issued patent.

Applicants agree that the subject matter claimed in the current application covers functionally active variants of hTERT.

However, it is respectfully submitted that a finding of obviousness-type double patenting is not permissible in the present circumstances. The present application has the earlier filing date. The priority date claimed in the issued patent is August 3, 1998. In contrast, the disclosure of the present application was first filed on November 19, 1997, and has a priority basis at least as early as May 6, 1997.

The particular hTERT sequences claimed in the 6,337,200 comprise an unpredictable subset of all possible hTERT sequences and variants. In particular, the patented variants necessarily have a deletion of at least 10 amino acids from region 192-323 or 415-450 of the hTERT sequence. The functional effect of these particular deletions were not predicted from the hTERT sequence alone, but were empirically determined in subsequent experiments. The particular deletions were found to be patentably distinct by the Patent Office in view of the native hTERT sequence disclosure in several of

the publications of record in the 6,337,200 patent. Accordingly, the subject matter of the issued patent is not obvious with respect to the present application<sup>3</sup>.

Since the present disclosure has an earlier filing date, it could not be challenged as obvious over the 6,337,200 patent *if that patent was filed by another party*. Under the new 20-year term provisions of 35 USC § 154(a)(2), no extension of patent term results from issuance of a patent on the present application. It is inappropriate and unfair to require applicants to file a terminal disclaimer with respect to a later-filed patent *just because the later-filed patent is their own*.

Withdrawal of this rejection is respectfully requested.

#### Request for Interview

Applicants respectfully request that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

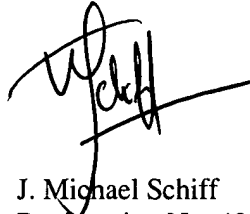
In the event that the Examiner determines that there are other matters to be addressed, applicants hereby request an interview by telephone. Please contact applicants' representative at the telephone number indicated below.

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<sup>3</sup> *In re Berg* 46 USPQ2d 1226 (Fed. Cir. 1998) is cited in MPEP § 804(II)(B)(1) as standing for the proposition that obviousness-type double patenting should be assessed as a two-way obviousness test if the issued patent has a later filing date. However, the patent at issue had the serial number 07/918,360, and so was filed before the term of the patent was set to run from the filing date of the priority application in 35 USC § 154(a)(2), effective for applications filed after June 7, 1995. A terminal disclaimer was required under the previous regime to prevent an unjustified timewise extension of the patent already issued. The same consideration does not apply under the new regime, because the 20-year term of a patent issuing from the application with the earlier filing date will necessarily expire before the 20-year term of the later-filed issued patent.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicants hereby petition for such relief. The Commissioner is hereby authorized to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139.

Respectfully submitted,



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## CHANGES MADE

USSN 09/432,503

Docket 018/063c

### ***Amendments to the Claims:***

41. (*Amended*) A method of increasing the proliferative capacity of a mammalian cell, comprising introducing into the cell a recombinant polynucleotide that encodes a telomerase reverse transcriptase protein, variant, or fragment having telomerase catalytic activity when complexed with a telomerase RNA,  
wherein ~~DNA having the sequence of~~ the polynucleotide hybridizes to DNA having the ~~sequence of~~ a sequence complementary to SEQ. ID NO:1 at 5°C to 25°C below  $T_m$  in aqueous solution at 1 M NaCl;  
wherein  $T_m$  is the melting temperature of double-stranded DNA having the sequence of SEQ. ID NO:1 under the same reaction conditions; and  
whereby introducing the recombinant polynucleotide into the cell increases the proliferative capacity of the cell.
42. The method of claim 41, wherein the cell is a human cell.
43. The method of claim 41, further comprising selecting the cell from other cells because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide.
44. The method of claim 43, wherein the cell is a human cell.
45. The method of claim 41, wherein the polynucleotide encodes a full-length, naturally occurring telomerase reverse transcriptase.
- ~~46. The method of claim 45, wherein the cell is a human cell.~~
47. The method of claim ~~44~~ 45, further comprising selecting the cell from other cells because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide.
48. The method of claim 41, wherein the polynucleotide encodes a telomerase reverse transcriptase having the amino acid sequence of SEQ ID NO:2.

49. The method of claim 48 wherein the cell is a human cell.
50. The method of claim 48 further comprising selecting the cell from other cells because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide.
51. The method of claim 50 wherein the cell is a human cell.
52. The method of claim 41, wherein the recombinant polynucleotide is an expression vector.
53. The method of claim 52 wherein the expression vector is an SV40 virus expression vector, an EBV expression vector, an ~~Autographa californica nuclear polyhedrosis virus~~ expression vector, a herpesvirus expression vector, or a vaccinia virus expression vector.
54. The method of claim 52 wherein the expression vector is a retrovirus expression vector.
55. The method of claim 52 wherein the expression vector is an adenovirus expression vector.
56. The method of claim 52 further comprising selecting the cell from other cells because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide.
57. The method of claim 52 wherein the cell is a human cell.